Vitamin C in Burn Resuscitation

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KEYWORDS

• Reactive oxygen species • Free radical • Ascorbic acid • Vitamin C • Burn

KEY POINTS

- Damage from reactive oxygen species significantly contributes to the increased resuscitative requirements after burn injury.
- Vitamin C is an inexpensive, readily available antioxidant.
- Preclinical and clinical studies demonstrate vitamin C can be an effective adjunct in burn resuscitation by decreasing overall fluid requirements and edema.
- Vitamin C appears to be well tolerated, but further investigation is needed to identify unanticipated effects from high-dose administration to burn patients.

INTRODUCTION

Proper fluid management in the immediate phase after significant burn injury is important for optimizing outcomes. The goal of burn resuscitation is to ensure adequate end-organ perfusion at the lowest physiologic cost. The pathophysiology of the massive fluid shifts that occur after burn injury and the underlying microvascular changes have been studied previously in an attempt to identify targets to reduce overall fluid requirements.[1–3] Increased capillary permeability results in the escape of fluid and protein from the intravascular into the interstitial space and is greatest in the first 8 hours after burn injury.[4] Compared with other forms of traumatic injury, the increased

The authors have nothing to disclose.

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Crit Care Clin 32 (2016) 539–546

http://dx.doi.org/10.1016/j.ccc.2016.06.003 **criticalcare.theclinics.com**

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resuscitative requirements after burn injury are largely due to intravascular volume losses from capillary leakage. Excess fluid can accumulate in any tissue bed, resulting in resuscitation-related morbidity. These morbidities include pulmonary edema, compartment syndromes (muscle compartments, abdomen, and the orbits), and even cerebral edema.

Various inflammatory mediators have been shown to contribute to increased vascular permeability after burn injury, but mediator-targeted therapies have largely been unable to significantly mitigate capillary leak and thus decrease the resuscitation volumes needed. Reactive oxygen species (ROS) have also been reported to make a significant contribution to the increased vascular permeability, and antioxidant therapy has been investigated as a potential therapy to decrease ROS-induced damage. However, the pathophysiology of ROS-mediated damage and its effect on vascular permeability is complex and requires further investigation.

PATHOPHYSIOLOGY: INCREASED CAPILLARY PERMEABILITY

Increased capillary permeability after burn injury is due to several mechanisms. Immediately after a burn, mast cells release histamine that increases the activity of xanthine oxidase, which is one of many pathways that contribute to the increased production of ROS observed after burn injury.[2] ROS are formed endogenously during the metabolism of oxygen and can be produced through a variety of different enzymatic pathways, including NADPH oxidase, xanthine oxidase, and endothelial nitric oxide synthase, and in the electron transport chain.[5] ROS have vital physiologic roles in cell signaling, immune defense, and vascular tone, among others, but can also damage proteins, lipids, and nucleic acids at higher concentrations and have been implicated in many disease processes, such as cancer, insulin resistance, and atherosclerosis.[6] ROS-induced endothelial damage to lipids and proteins of cell membranes has been shown to contribute to the increased capillary leakage associated with burn injury.[7–10]

ANTIOXIDANT THERAPY

Therapies targeted at blocking the action of xanthine oxidase to reduce the formation of ROS have shown improved survival in preclinical burn models only when inhibitors are administered before burn injury,[11] which suggests that redundant formation pathways and enzyme activity create a complex barrier for effective targeting of ROS production. Therefore, a better strategy for preventing or minimizing increases in capillary permeability following burn injury might be to attenuate ROS-induced damage by removing ROS from circulation with a scavenger.[2,12] Therapies scavenging ROS as an adjunct in burn resuscitation could minimize capillary leak, and in turn, reduce the resuscitative requirements of large burns and minimize edema.

Because excess ROS is damaging to lipids, proteins, and nucleic acids, multiple endogenous systems exist to reduce ROS levels and include enzymes such as superoxide dismutase, catalase, peroxiredoxin, and thioredoxins.[12] For example, superoxide dismutase is part of an antioxidant system shown to decrease lipid peroxidation, a process that propagates chain reaction production of ROS.[13] However, the excessive ROS levels produced following a burn injury overwhelm endogenous systems, and exogenous ROS scavengers are needed to reduce ROS levels. Antioxidants are a class of effective ROS scavengers that act as reducing agents and become oxidized to neutralize ROS. Examples of nonenzymatic antioxidants include vitamins (such as C and E), minerals (such as selenium), and glutathione.[14] Several antioxidant therapies have been evaluated for their efficacy at reducing the capillary permeability after

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burn injury. Early administration of the histamine-blocker cimetidine reduced resuscitation requirements in thermally injured animals,[15] and further study suggested antioxidant, ROS-scavenging activity may be responsible for the beneficial effects of cimetidine.[2]

VITAMIN C

Ascorbic acid, or vitamin C, is a naturally occurring, essential nutrient that acts as an effective antioxidant and ROS scavenger. Vitamin C is highly water soluble and therefore cannot directly scavenge ROS within the cell membrane, but rather vitamin C removes ROS present in the extracellular space, thus regenerating vitamin E as a potent cell membrane ROS scavenger.[14] Vitamin C also protects circulating cells (erythrocytes and leukocytes) from ROS damage.[16] The high water solubility of vitamin C allows excess to be excreted by the kidney, preventing toxic accumulation.[17] The antioxidant effects of vitamin C have been studied as an adjunct in treating sepsis and ischemia/reperfusion injuries, where it was shown to improve tissue oxygenation and mitigate subsequent organ dysfunction.[18,19]

VITAMIN C: PRECLINICAL BURN STUDIES

Early reports of using vitamin C in burn injury demonstrated benefit in treating ocular alkali burns in a rabbit model[20] and in attenuating burn wound tissue necrosis when administered in the intraperitoneal space.[21] Preclinical studies have since evaluated the utility of vitamin C as an adjunct to burn resuscitation with the objective of decreasing total intravenous fluid requirement after a large burn (**Table 1**). In a guinea pig model of large burn (70% total body surface area [TBSA] burn), administration of high-dose vitamin C (14.2 mg/kg/h) effectively reduced the total fluid requirement while not compromising the hemodynamic parameters of the animals.[16,22–25] In fact, the cardiac output increased in direct proportion to a hematocrit decrease when vitamin C was administered within 6 hours of burn injury and for a duration of at least 6 hours.[4] Burn wound edema was significantly decreased after vitamin C administration,[16,22–25] and further studies demonstrated that the decrease in the strongly negative interstitial fluid hydrostatic pressure, lymph flow, and loss of protein from the interstitial space were, at least in part, responsible for the observed decrease in edema.[26,27] These findings have been reproduced in a large animal burn model where sheep (40% TBSA burn) given high-dose vitamin C (15 mg/kg/h) needed 30% less fluid at 6 hours and approximately 50% less fluid at 48 hours while maintaining adequate hemodynamics.[28] Furthermore, animals demonstrated decreased levels of plasma thiobarbituric acid reactive substances, an index of reduced lipid peroxidation.[28] Although most of the preclinical studies of vitamin C in burn models have been from one group, they nonetheless provide the framework for clinical investigations.

VITAMIN C: CLINICAL BURN STUDIES

To date, only 2 clinical studies have examined the utility of vitamin C as an adjunct in burn resuscitation. The first, published in 2000[29] by the same group that performed most of the preclinical studies, prospectively randomized 37 patients with greater than 30% TBSA thermal injury to isotonic and colloid fluid resuscitation with or without high-dose vitamin C (66 mg/kg/h). The Parkland formula was used to calculate expected fluid requirements, adding 5% albumin during the second and third 24 hours after injury. The vitamin C group required 45% less fluid at the 24-hour mark and demonstrated decreased lipid peroxidation, as evidenced by decreased serum

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Table 1
Summary of preclinical studies of vitamin C in burn models

Lead Author, Year	Animal	Resuscitation (mL/kg/TBSA)	Vitamin C Dose (mg/kg/h)	Vitamin C Timing (h Postburn)	Findings in Vitamin C Patients
Matsuda et al,[23] 1991	Guinea pig	1–4	7–28.3	0.5–24	↑CO, ↓Hct, ↓skin H_2O content
Matsuda et al,[22] 1992	Guinea pig	1–4	7	0.5–24	↑CO, ↓Hct, ↓skin H_2O content
Matsuda et al,[26] 1992	Dog	Maintenance	14.2	0.25–6	↓Protein loss, ↓lymph flow
Tanaka et al,[4] 1992	Guinea pig	1–4	14.2	2–4, 2–8, 2–24	↑CO, ↓Hct
Tanaka et al,[24] 1995	Guinea pig	1–4	14.2	2–24	↑CO, ↓Hct
Matsuda et al,[16] 1995	Guinea pig	1–4	14.2	0.5–4, 0.5–8, 0.5–24	↑CO (peak at 8 h), ↓Hct (best at 8 h)
Tanaka et al,[25] 1997	Guinea pig	1–4	14.2	0.5–24	↑CO, ↓Hct, ↓burned skin H_2O content
Sakurai et al,[17] 1997	Guinea pig	1–4	14.2	6–24	↑CO, ↓Hct, ↓burned skin H_2O content
Tanaka et al,[27] 1999	Rat	?	33 (66 bolus)	(−)0.5–0.5	↓Pif, ↓total tissue H_2O content
Dubick et al,[28] 2005	Sheep	4	15	1–24	↓Net fluid, ↓plasma TBARS

Abbreviations: CO, cardiac output; Hct, hematocrit; Pif, interstitial fluid hydrostatic pressure; TBARS, thiobarbituric acid.

malondialdehyde levels compared with the non-vitamin C group. Respiratory function was also improved in the vitamin C patients with improved oxygenation and decreased duration of mechanical ventilation. However, this preliminary study did not show a significant difference in mortality.

The second clinical study[30] was a retrospective analysis of patients treated over a 3-year period (2007–2009) who were split into a control group, who were resuscitated according to the Parkland formula, and an experimental group, whose resuscitation strategy included the Parkland formula plus the volume required to achieve a vitamin C dose of 66 mg/kg/h, which for a 70-kg patient was an additional 168 mL/h. The 24-hour fluid requirements were 25% less in the vitamin C–treated subjects, and a diuresis was noted in this group as well, which decreased the net balance of fluid. Even though this study did not demonstrate improved respiratory function or improved mortality, which could be attributed to the small sample size, it did demonstrate that vitamin C could be used to decrease the overall resuscitation volume needed without an increased risk of renal failure or other infectious processes.

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VITAMIN C: MECHANISMS OF ACTION IN BURN INJURY

In addition to ROS scavenging, regeneration of vitamin E, and attenuation of lipid peroxidation, vitamin C functions through mechanisms specific to burn injury to decrease fluid requirements and wound edema. Because a reduced volume of isotonic fluid is required for burn patients treated with vitamin C, the dilutional hypoproteinemia causing decreased oncotic pressure and subsequent fluid shift into nonburned tissue is minimized,[31] evidenced in preclinical studies by a reduced water content in unburned skin.[22] Wound edema is further decreased by vitamin C infusion through the inhibition of collagen denaturation and enhancement of hyaluronic acid removal, both of which have been shown to promote wound edema.[27,32,33] In addition, vitamin C affords protection to burned tissue capillary endothelium, which has been compromised by thermal injury, by scavenging ROS from the extracellular space.[4] Lower resuscitation volumes are often associated with a reduced incidence of intra-abdominal hypertension, which, in turn, has the potential to prevent abdominal compartment syndrome.[34,35]

VITAMIN C: SIDE EFFECTS

Vitamin C is highly hydrophilic and is readily excreted by the kidneys, thereby reducing potential toxicity that would be associated with elevated circulating concentrations. Literature evaluating the potential toxicity profile or side effects from high-dose vitamin C therapy is scarce, possibly because of the intravenous administration being so well tolerated. Because excess vitamin C is excreted by the kidneys, osmotic diuresis and worsening acute kidney injury have been identified as side effects in burn patients.[36] The intravenous formulation of vitamin C is hyperosmolar,[30] unless specific effort is made to create an isotonic, diluted solution.[29] Osmotic diuresis necessitates extra precautions be taken to ensure that acute kidney injury or hypovolemia does not occur as a result in resuscitated burn patients, so monitoring of serial hematocrit levels and evaluation for clinical signs of hypovolemia are vital.[30] Absorbed vitamin C is metabolized to threose and oxalic acid, so oxalate nephropathy from a buildup of water-insoluble calcium oxalate has been demonstrated when vitamin C has been used as an alternative therapy for cancer and amyloidosis.[37,38] Oxalate nephropathy has also been observed in the postmortem examinations of a small number of burned patients treated with high-dose (66 mg/kg/h) vitamin C as a rescue therapy during difficult resuscitations.[39] Hyperoxaluria from high-dose vitamin C can worsen existing kidney injury or delay kidney recovery.[36] Renal toxicity should be carefully monitored in future studies, especially in patients with pre-existing kidney injury.

Another concern with vitamin C administration is the false elevation of point-of-care (POC) glucose measurements that has been reported.[40] In vitro studies have established that vitamin C interferes with electrochemical assays used to test POC glucose measurements[41] and that standard laboratory measurements have been necessary to determine accurate glucose levels for up to 24 hours after discontinuation of vitamin C infusion.

VITAMIN C: DOSING

The recommended adult daily intake of vitamin C is 75 mg for women and 90 mg for men. Because of high water solubility and low metabolism, daily oral doses of up to 10 g seem to be well tolerated. However, the optimal dosing of vitamin C in burn resuscitation has not been determined. Preclinical studies have examined doses of vitamin C ranging from 7 to 28.3 mg/kg/h and found efficacy in reducing resuscitation volume

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with a dose of 14.2 mg/kg/h.[23] The dose chosen for the 2 existing human studies was 66 mg/kg/h,[29,30] which is roughly 5-fold higher than that used in guinea pigs (14.2 mg/kg/h). It is unclear why 66 mg/kg/h was chosen for clinical studies, especially with respect to preclinical investigations that used substantially lower doses. The justification behind a higher dose for human studies seems to rely on the fact that larger mammals may need larger doses of vitamin C due to the more complex nature of ROS generating systems,[42] but controlled, dose-response studies have not yet been conducted to determine if lower doses would be equally effective at improving outcomes. Although a vitamin C dose of 66 mg/kg/h has been well tolerated in the existing human studies, further investigation is needed because there may be a dose-dependent increase in the incidence of renal toxicity, especially in the presence of existing kidney injury.[36] For a 70-kg patient, 66 mg/kg/h would be roughly 4.6 g/h, and over a 24-hour resuscitation period could approach a total dose of 110 g of vitamin C, potentially increasing the risk for adverse effects.

SUMMARY

Vitamin C holds potential as a powerful adjunct in burn resuscitation but a scarcity of definitive literature demonstrating therapeutic efficacy on clinical outcomes, combined with an incompletely understood side-effect profile, limits widespread implementation by burn centers. However, studies to date have shown that vitamin C may be safe and decreases fluid requirement in the acute phase after burn injury. Robust multicenter trials are needed to fully characterize the potential impact of vitamin C as an adjunct in burn resuscitation.

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